PB88-176029

Health and Environmental Effects Profile for Cyclohexanol

(U.S.) Environmental Protection Agency
Cincinnati, OH

Apr 85

U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/600/X-85/109	2.	3. RECIPIENT'S ACCESSION NO. PB88 176029/AS
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Cyclohexanol		5. REPORT DATE April 1985 6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

The Health and Environmental Effects Profile for cyclohexanol was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for cyclohexanol.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for cyclohexanol is 1000.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified 20. SECURITY CLASS (This page) Unclassified	21. NO. OF PAGES 42 22. PRICE PC A03/MF A01 $6.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB88-176029

EPA/600/X-85/109
April 1985

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CYCLOHEXANOL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BOD	Biochemical oxygen demand
bw	Body weight
CS	Composite score
FEL	Frank effect level
GC	Gas chromatography
GC/MS	Gas chromatography/Mass spectrometer
i.v.	Intravenous
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RNA	Ribonucleic acid
RQ	Reportable quantity
RV_d	Dose rating value
RV_e	Effect rating value
s.c.	Subcutaneous
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Cyclohexanol is a secondary alcohol also known as cyclohexylalcohol, hexahydrophenol or hydrophenol (Verschueren, 1983). This compound is also known by its trade names, hexalin and hydralin (Verschueren, 1983). The structure of cyclohexanol is given below:

It has an empirical formula of $C_6H_{12}O$ and a molecular weight of 100.16. The Chemical Abstract Service (CAS) Registry number for this compound is 108-93-0.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Cyclohexanol is a colorless, oily, hygroscopic liquid with a camphor-like odor (Hawley, 1977). Some of the physical properties of cyclohexanol are given below (Fisher and Van Peppen, 1979; Vershueren, 1983; MacKay et al., 1982).

Melting point:	25.15°C
Boiling point:	161.1°C
Density in g/mℓ:	0.9493_4^{20}
Vapor pressure at 25°C:	1.1 mm of Hg
Relative vapor density (air=1):	3.45
Solubility in water at 20°C:	36,000 mg/ℓ
Henry's Law Constant (H) at 20°C:	2.5×10^{-6} atm.m³/mol
Log octanol/water partition coefficient:	1.23
Conversion factor:	1 ppm = 4.163 mg/m³ at 20°C and 1 atmosphere

Cyclohexanol shows most of the typical chemical reactions of secondary alcohols. It is oxidized to cyclohexanone under mild conditions and to adipic acid under strong conditions. It can be dehydrated to cyclohexane. It reacts with organic acids to form esters and with halogen acids to form acid halides (Fisher and Van Peppen, 1979).

1.3. PRODUCTION DATA

Cyclohexanol is prepared commercially by catalytic air oxidation of cyclohexane or by the catalytic hydrogenation of phenol, although the former process is used predominantly. Both technical and high grade commercial products are available in the market (Fisher and Van Peppen, 1979).

In 1977, seven companies manufactured cyclohexanol in nine different locations in the United States. With only five of the seven companies reporting the manufactured volume, the total cyclohexanol production ranged from 470-2200 million pounds in 1977 (U.S. EPA, 1977). According to the data available from USITC (1983), only the following four companies manufactured cyclohexanol in the United States in 1982:

Allied Corp.	Hopewell, VA
Badische Corp.	Freeport, TX
E.I. DuPont Co.	Orange, TX Victoria, TX
Monsanto Co.	Luling, LA Pensicola, FL

The Directory of Chemical Producers (SRI, 1984) lists the same companies, with the exclusion of Monsanto Company and the inclusion of Nipro, Inc., Augusta, GA as the manufacturers of cyclohexanol in the United States as of January, 1984. The recent production volume for this chemical in the United States was not available.

1.4. USE DATA

The most important use of cyclohexanol in the United States is in the production of adipic acid, which is used in the manufacture of nylon. Other major uses of cyclohexanol include the production of E-caprolactam (used in the manufacture of nylon polymer) and the manufacture of esters that are used as plasticizers. Cyclohexanol is also used as a solvent for lacquers, shellacs, varnishes and, in the textile industry, as a dye solvent and Kier boiling acid. As a stabilizer and homogenizer, it is used in soaps and synthetic detergents (Fisher and Van Peppen, 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

No experimental information regarding the fate and transport of cyclohexanol in the ambient atmosphere were located in the literature cited in the Appendix. Based on some of the physical properties and chemical reactions of cyclohexanol, some predictions about the atmospheric fate and transport can be made. From the abstract of a Russian study (Korotkova et al., 1981), it can be concluded that cyclohexanol is oxidized by ozone in the atmosphere. However, in the absence of quantitative data on the rate of this reaction, the half-life for this reaction in the atmosphere cannot be estimated. Oxidation of cyclohexanol by hydroxyl radicals in the atmosphere is another possible fatedetermining process for which no qualitative or quantitative rate data are available. Other than chemical/photochemical processes, cyclohexanol, like any other chemical, may be partially removed from the atmosphere by physical processes, especially by wet and dry deposition. The high aqueous solubility of cyclohexanol would indicate that both rainout and washout may play important roles in removing this chemical from the atmosphere. The longer time a chemical survives the chemical and physical removal processes, the longer distances it is expected to be transported in the atmosphere. Since the rate of atmospheric removal through chemical/physical processes is not known in the case of cyclohexanol, it is not possible to estimate the distance it may travel through the atmosphere from its source of emission.

2.2. WATER

The fate of cyclohexanol in aquatic media has been studied more than its fate in atmospheric and soil media. Most investigators, however, studied its degradation by microbiological processes. Several pure cultures of microorganisms isolated most frequently from soil, water, estuarine and

marine mud have been shown to biodegrade cyclohexanol. The pure cultures that are capable of degrading cyclohexanol are shown in Table 2-1.

Although these pure culture studies indicate that cyclohexanol is biodegradable with the isolated microorganisms, they are not useful in assessing the biodegradability of cyclohexanol in the natural environment. Several authors studied the biodegradability of cyclohexanol with mixed cultures. Using a mixed culture capable of degrading phenol rapidly, Chambers et al. (1963) showed slight biodegradation (0.4% of theoretical BOD in 3 hours) of cyclohexanol. The degradation of cyclohexanol with acclimated activated sludge was shown by Pitter (1976) and Patel and Patel (1977). A 96% removal of cyclohexanol in water was observed in 5 days with acclimated activated sludge in the presence of mineral salts medium at 20°C (Pitter, 1976). Other researchers used inoculum from polluted surface and wastewater to show the possibility of biodegradation of cyclohexanol (Dore et al., 1975; Wagner, 1974). The microbial degradation of cyclohexanol in aqueous medium using sewage as seed was reported by Heukelekian and Rand (1955). A 3% theoretical BOD removal was noted on incubation for 5 days at 20°C. The degradation of cyclohexanol in natural water by using models of low-running reservoirs and flowing water was studied by Lobchenko et al. (1975). Microbial degradation was assessed as one of the important fate-determining processes; however, the rates of the degradation processes were not available from the abstract of this study. Therefore, no quantitative assessment about the importance of biodegradation or any other processes in natural aqueous media could be made.

The rate of oxidation of cyclohexanol by peroxy radicals in aqueous media was reported to be 0.17 ℓ mol^{-1} sec^{-1} by Hendry et al. (1974). Assuming the peroxy radical concentration of 10^{-9} M in natural water (Mill, 1982), the half-life for this process is estimated to be ~130 years.

TABLE 2-1

Species of Pure Cultures of Microorganisms
Capable of Degrading Cyclohexanol

Species of Pure Culture	Reference
Pseudomonas sp.	Anderson et al., 1980
M-convolution R22	Beam and Perry, 1974
Nocardia sp.	Stirling and Watkinson, 1977
Pseudomonas sp.	Tanaka et al., 1977
Nocardia sp.	Perry, 1980
Pseudomonas sp.	Bisz-Konarzewska, 1978
Corynebacterium eugi	Ohta et al., 1984
Nocardia sp.	Donoghue et al., 1976

Therefore, oxidation of cyclohexanol by peroxy radicals in natural water may not be a significant fate-determining process. Information pertaining to the importance of direct photolysis of cyclohexanol in natural aquatic media in determining its aquatic fate was not located in the available literature as cited in the Appendix.

Limited information concerning the volatility of cyclohexanol from aquatic media was found in the literature. If the reaeration rate ratio of cyclohexanol is assumed to be 0.013 (MacKay et al., 1982) and the oxygen reaeration rates in representative water bodies are assumed to vary from 0.19-0.96 day^{-1} (Mabey et al., 1981), the half-life for the evaporation of cyclohexanol can be estimated to vary from about 56-281 days. Therefore, based on the half life and Henry's Law Constant (Cited in Setion 1.2.), volatilization does not appear to be a significant environmental process.

2.3. SOIL

Although no comprehensive study regarding the fate and transport of cyclohexanol in soil is available, some qualitative speculation about these processes can be made. Based on its biodegradability in aqueous media, it is likely that biodegradation will play an important role in determining its fate in soil. The evaporation of cyclohexanol from soil is likely to be insignificant. The soil sorption coefficient (K_{oc}) for cyclohexanol in a soil containing 1% organic matter is estimated to be 0.24 from the sorption equation ($\log K_{oc} = 0.72 \log K_{ow} + \log f_{oc} + 0.49$, where K_{ow} is the octanol/water partition coefficient and f_{oc} is the fraction organic content) of Schwarzenbach and Westall (1981). Noting the high solubility and the estimated low soil sorption of cyclohexanol, it is speculated that this compound may leach significantly from soil.

3. EXPOSURE

The only report on the level of cyclohexanol in air is available from the abstract of a Russian study (Mandzhgaladze and Kuchukhidze, 1972). These authors sampled air inside a caprolactam fiber production plant and reported the detection of cyclohexanol at concentrations higher than the maximum allowable limit, particularly in the spinning area and during the summer months.

No water monitoring data for cyclohexanol are available in STORET. In a Russian study (Savelova et al., 1962), the concentration of cyclohexanol in wastewaters from a caprolactam manufacturing facility was reported to be 3.5 mg/ℓ. Several authors reported the detection of cyclohexanol in leachates and groundwater from waste disposal sites and the results of their findings are shown in Table 3-1.

Finally, Tang et al. (1983) reported the detection of cyclohexanol as one of the several compounds in fried chicken flavor. No information on the level of cyclohexanol in any other food was available.

TABLE 3-1

Cyclohexanol Levels in Leachates and Groundwaters

Nature of Water	Origin of Water	Concentration of Cyclohexanol	Reference
Leachate	low level radioactive waste disposal sites at Maxey Flats, KY and West Valley, NY	0.24-1.2 mg/ℓ	Francis et al., 1980; Francis, 1982
Groundwater	aquifer polluted by organic waste dump from Western Suburbs of Melbourne, Australia	detected but not quantified	Stephan et al., 1981
Groundwater	contaminated waste dump sites in the Netherlands	<1 mg/ℓ	Zoeteman et al., 1981
Leachate	municipal waste dump sites in the Netherlands	detected but not quantified	Harmson, 1983
Groundwater	land disposal site near Norman, OK	0.001 mg/ℓ (estimated)	Dunlap et al., 1975, 1976

4. PHARMACOKINETICS

4.1. ABSORPTION

Cyclohexanol produces toxic effects when exposure occurs by oral, skin, parenteral or inhalation routes (Rowe and McCollister, 1982). Cyclohexanol has been used to aid in the penetration of externally applied drugs through the skin (Opdyke, 1975).

4.2. DISTRIBUTION

When applied to rabbit skin over several days, cyclohexanol was observed to cause local injury including localized ulcers and thickening of the skin, narcosis, central nervous system irritation, hypothermia and considerable lacrimation (Treon et al., 1943a). The authors felt that lacrimation was due to transport of cyclohexanol from the point of application to the eyes through the bloodstream rather than direct action of the vapor on the eyes, since care was taken to ensure that vapors did not reach the area of the head.

Martis et al. (1980) administered an i.v. dose of 328 mg cyclohexanol/kg bw to a beagle dog. Blood samples were collected in heparinized tubes at stated time intervals for a 24-hour period. Cyclohexanol concentrations in plasma were determined by GC. The plasma concentration of cyclohexanol was found to decline in a mono-exponential manner with an elimination half-life of 99 minutes. The apparent distribution volume was calculated as 1.2 ℓ/kg and the total body clearance rate was 8.8 mℓ/kg/min.

4.3. METABOLISM

Elliot et al. (1959) treated two adult chinchilla doe rabbits by gavage with 260 mg/kg ^{14}C-cyclohexanol. Urine collected for 2 days after dosing was subjected to acid hydrolysis followed by paper chromatography. The metabolites found (expressed as a percentage of administered dose) were

cyclohexanol (animal one, 58%; animal two, 64.5%), transcyclohexane-1,2-diol (animal one, 7.3%; animal two, 5.5%), and cyclohexanone (considered by the authors to be an artifact) (animal one, 5.3%; animal two, 6.1%). All of these metabolites were present in urine as conjugates with glucuronic acid. The sum of the metabolites recovered after 2 days was 65.3% of the administered radioactivity for animal one and 70.0% for animal two.

Cyclohexanol is oxidized reversibly by alcohol dehydrogenase from horse (Winer, 1958), rat (Merrit and Tomkins, 1959; Cronholm, 1983; Skurko and Papova, 1977) and human (Wagner et al., 1983) liver fractions. Cyclohexanol was not found to be a significant substrate for alcohol dehydrogenase isoenzymes from the following endocrine tissues: human placenta, rat ovary, rat testis, and rat adrenal gland (Ferguson et al., 1966).

Cyclohexanol was found as a minor metabolite when 100 mg of sodium cyclamate was incubated with a homogenized preparation of rat liver for 90 minutes at 37°C (Kojima and Ichibagase, 1968).

4.4. EXCRETION

Cyclohexanol was given by gavage to two adult chinchilla doe rabbits (Elliot et al., 1959) and urine was collected for 2 days after dosing. Sixty-five percent of the administered dose was detected as the glucuronide conjugate in the urine.

Beagle dogs received an i.v. dose of 284 mg cyclohexanone/kg bw/day for 18 or 21 consecutive days (Martis et al., 1980). Blood and urine samples were taken at predetermined time intervals following cyclohexanone administration on the first and last day of the study. Cyclohexanol concentrations in plasma were determined by GC. Cyclohexanol was formed rapidly after cyclohexanone administration and reached a peak concentration in plasma within 30 minutes. Between 74 and 100% of the administered cyclohexane was

converted to cyclohexanol. Approximately 60% of the administered dose was detected in the urine after 24 hours as the glucuronide conjugate of cyclohexanol. Less than 1% of the administered dose was recovered in the urine as free cyclohexanone or cyclohexanol.

Cyclohexanol was found in the urine of eight human subjects (aged 18-30 years) who had been exposed to atmospheric cyclohexanol in the work place (Mutti et al., 1981). The amount of cyclohexanol taken up by blood from the air was estimated by determining the difference in atmospheric and alveolar concentrations of cyclohexane. Urinary samples were taken at the end of the exposure and again after 6 hours. Cyclohexanol excreted in the urine (determined by gas chromatography) was only 1% of the absorbed dose of cyclohexane and was poorly related to the level of exposure.

In other studies (Perbellini et al., 1980, 1981a,b,c), cyclohexanol was found in the urine of workers in a shoe factory who had been exposed to cyclohexane in the air. The collected urine was subjected to either acid or enzymatic (β-glucuronidase) hydrolysis, and was analyzed by GC and a GC/MS. Cyclohexanol was found after both acid and enzymatic hydrolysis, suggesting that it is excreted as both a glucuronide and a sulfate ester.

Cyclohexanol was found in the urine of humans, rats and rabbits after oral doses of sodium cyclamate (Kojima and Ichibagase, 1968) and in humans, rats, rabbits and guinea pigs after doses of cyclohexanone (itself a metabolite of cyclamate) (Renwich and Williams, 1972). In all species cyclohexanol was detected primarily as a glucuronide conjugate.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of cyclohexanol were not located in the available literature as cited in the Appendix.

5.2. MUTAGENICITY

Collin (1971), in a study on the cytogenetic effects of cyclamate, cyclohexanone and cyclohexanol, observed achromatic regions, breaks and deletions when karyotype analysis was performed on human leukocytes grown in culture medium containing 10^{-2}, 10^{-3} or 10^{-4} M cyclohexanol. No statistical analysis was performed in the study and the cytogenic effects observed did not appear to be dose-related.

Goncharova (1970), in an abstract of a Russian study, treated male Drosophila melanogaster with cyclohexanol at 0.1 mℓ/100 mℓ for 3 days with no observable effect on the frequency of lethal mutations. In a companion study, Goncharova and Laryutina (1970) found no effect on the frequency of recessive lethal mutations in male D. melanogaster after γ- and X-ray treatments of fruit flies pretreated with 0.1 mℓ/100 mℓ cyclohexanol for 3 days. No further experimental details were provided for either study.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of cyclohexanol were not located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Gondry (1973) fed diets containing 1.0% cyclohexanol to pregnant mice. An increase in the mortality rate of the offspring for the first 21 days of life was observed. The mortality in first generation treated offspring was 14.1% and in second generation treated offspring was 53.5% (controls, 11.9%;

strain TB mice). In MORI strain mice, the mortality in first generation treated offspring was 43.1% (controls, 12.2%). Additional information regarding this study was not reported in the available review (Rowe and McCollister, 1982).

Cyclohexanol was administered to 20 male gerbils (s.c. injection, 15 mg/kg/day for 21 days) and 20 male house rats (s.c. injection, 15 mg/kg/day for 37 days) (Tyagi et al., 1979). The weights of testes, epididymides, seminal vesicles and ventral prostate were significantly reduced in treated animals ($p<0.01$) with the exception of the seminal vesicles in the gerbils. Degenerative changes consisting of loss of type A spermatogonia, spermatocytes, spermatids and spermatozoa were observed in the seminiferous tubules of treated gerbils and rats. The total glycogen content of the testes and the protein, RNA and sialic acid contents of testes, epididymides and seminal vesicles were significantly ($p<0.01$) reduced in treated animals of both species. Cholesterol content and alkaline phosphatase activity in testes were significantly ($p<0.01$) increased in treated animals. Total body weights and thyroid and adrenal gland weights were not significantly different from controls.

When cyclohexanol was administered by gavage to 30-day-old male Sprague-Dawley rats (455 mg/kg/day for 7 days) (Lake et al., 1982), relative testes weights (g/100 g bw) were not significantly different from controls when analyzed by the Student's t-test.

Cyclohexanol was administered to 10 male rabbits by gavage (25 mg/kg/day for 40 days, olive oil carrier) (Dixit et al., 1980). Five control animals received olive oil alone. The effects in rabbits were similar to those observed in gerbils and rats: weights of testes and epididymides were significantly reduced ($p<0.01$); loss of type A spermatogonia, spermatocytes, spermatids and spermatozoa was observed; total glycogen, protein, RNA acid

phosphatase and sialic acid levels were reduced ($p<0.01$) and cholesterol levels were increased ($p<0.01$) in rabbit testes. Leydig cells were affected adversely. The lumen of both the cauda epididymis and vas deferens was devoid of sperm. Five of the treated rabbits were allowed a 70-day recovery period, after which normal spermatogenesis was observed.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic toxicity of cyclohexanol were not located in the available literature as cited in the Appendix. Studies on the subchronic toxicity of cyclohexanol administered by inhalation are available. One is from the early literature (Treon et al., 1943a) and the others are Russian studies (Dobrinskii, 1964; Voronin and Usol'tseva, 1972) mentioned in other reviews of the literature (Opdyke, 1975; Rowe and McCollister, 1982).

Treon et al. (1943a) exposed rabbits (four animals/group) to various concentrations of cyclohexanol in the air (1229, 997, 272 or 145 ppm) for 6 hours/day, 5 days/week for 5-11 weeks. At 1229 ppm for a total exposure time of 150 hours, the authors observed 50% mortality, accompanied by narcosis, incoordination, conjunctival congestion and irritation, salivation, ear-vein distension and weight loss. At 997 ppm for a total of 330 hours, 50% mortality was again observed, accompanied by other effects as described above. At 272 ppm for a total of 300 hours, no mortality was observed. Other effects included a slight conjunctival irritation and a slight ear-vein distension. At 145 ppm for a total of 300 hours, external evidence of toxicity was not apparent. The rabbits exposed to the two lowest doses gained weight throughout the course of the study. Unspecified slight microscopic changes in the liver and kidney of rabbits exposed to 145 ppm were reported, with a general statement for all compounds tested in this study that these changes were more severe at higher doses.

One monkey exposed to 693 ppm cyclohexanol in air for 50 periods of 6 hours each showed evidence of microscopic changes in the heart, lung, liver and kidneys (Treon et al., 1943a).

Rats exposed to cyclohexanol (0.149 and 0.014 ppm), 24 hours/day for 87 days (Dobrinskii, 1964), followed by a 6-day period on 20% of normal rations, reportedly showed effects at the highest dose level. The ascorbic acid content of the liver was increased, cholinesterase activity was decreased and changes were observed in the "interrelationship of the chronaxie of the extensor and flexor muscles" (decreased after week 7).

Voronin and Usol'tseva (1972) reported that hypoxia was observed in rats exposed to 43 mg/m³ cyclohexanol 5-6 hours/day for 100 days. Copper levels in the lungs and serum were decreased, and iron and nickel levels were increased.

In another Russian study (Savelova and Sergeev, 1970), rats received daily oral doses of cyclohexane, cyclohexanol, cyclohexanone, and cyclohexanone oxime or a combination of the four. Actual dosages were not stated, but the compounds were given at the maximum permissible concentration or 25% of the maximum permissible concentration, or at the minimum effective concentration. All dosage levels disturbed conditioned reflexes in all experimental animals, and microscopic degenerative changes were noted in the central nervous system. The cumulative toxicity of the four compounds was greater than what would be expected from the separate effects of each compound.

After oral cyclohexanol administration to 10 male rabbits (25 mg/kg/day for 40 days), a depletion of serum protein contents compared with controls was observed (Dixit et al., 1980). Serum cholesterol, phospholipids, triglycerides and bilirubin were all elevated ($p<0.01$), as were pyruvate

transaminase and alkaline phosphatase activities ($p<0.01$). Blood sugar levels and blood urea levels did not appear to be affected. Half the treated animals were allowed a 70-day recovery period after which total serum protein, triglycerides and pyruvate transaminase activity were at levels comparable to levels observed in control animals. Total cholesterol, phospholipids, bilirubin and phosphatase enzyme activity levels exhibited no significant tendency to return to pretreatment levels, a finding which led the authors to suggest that a metabolic disorder at the intracellular level and an interference in the formation of adrenal steroids may have been induced. Only degranulation within the hepatocytes was observed upon histological examination of liver biopsies.

In a similar study using gerbils (20 males) and house rats (20 males) (15 mg/kg/day for 21 and 37 days, respectively), no changes in either serum protein or serum cholesterol levels were observed in either species (Tyagi et al., 1979). Alkaline phosphatase and serum transaminases were also within normal ranges.

Perbellini et al. (1981b) administered 200 mg/kg cyclohexanol i.p. to rats for 13 weeks. They found no evidence of motor impairment, incoordination, ataxia or abnormalities in electrophysiological measurements. Experimental details were not reported.

Cyclohexanol was administered by stomach tube to 30-day-old male Sprague-Dawley rats at a dose level of 455 mg/kg/day for 7 days (Lake et al., 1982). An increase in relative liver weights was observed but there was no apparent effect on relative kidney weights. The hepatic activities of biphenyl 4-hydroxylase, 7-ethoxycoumarin O-deethylase and aniline 4-hydroxylase were stimulated.

5.6. OTHER RELEVANT INFORMATION

The oral LD_{50} of cyclohexanol in rats was reported to be 2.06 g/kg (Smyth et al., 1962) and the minimum lethal oral dose in rabbits was 2.2-2.6 g/kg (Treon et al., 1943b). The minimum lethal dose when applied to rabbit skin was 12.4-22.7 g/kg (Treon et al., 1943b). Rats have been found to tolerate exposure to concentrated cyclohexanol vapor for a maximum of 8 hours without the occurrence of any deaths (Smyth et al., 1962). The intravenous LD_{50} in the mouse has been reported as 0.27 g/kg (Northover and Verghese, 1962; Zagradnik et al., 1962) and the intramuscular LD_{50} has been given as 1.0 g/kg (Northover and Verghese, 1962).

In a Russian study (Myasoedova, 1968), cyclohexanol administered to mice and rats (route unspecified) at toxic levels caused motor activity inhibition, flaccidity, clinico-tonic spasms and death. Toxic levels of cyclohexanol given orally to rabbits produced "ataxia, lethargy, collapse, narcosis, loss of reflexes, and death" (Treon et al., 1943b). No convulsions were observed in rabbits. Cyclohexanol also decreased arterial pressure on anesthetized cats and caused local irritation of the skin and mucous membranes of unspecified animals (Myasoedova, 1968).

Cyclohexanol had cardioplegic effects on intact anesthetized rats, isolated guinea pig hearts, isolated rabbit atria (Smookler and Defeo, 1962) and isolated frog hearts (Myasoedova, 1968).

Oral administration of cyclohexanol to rabbits at toxic levels produced massive coagulation necrosis in the heart, lung, liver, kidney and brain (Treon et al., 1943b), and widespread vascular damage was also observed. In animals that survived smaller oral doses of cyclohexanol, low-grade chronic inflammatory changes were observed in the bronchi, alveolar septae and

pulmonary vessel walls. In the liver, there were some degeneration and areas of parenchymal regeneration. The kidney exhibited glomerulo-tubular nephritis.

In a study on the molecular basis of action of various alcohols, McCreary and Hunt (1978) found that the effective dose of cyclohexanol required to produce "ataxia 2" in male Sprague-Dawley rats was 4.0 mmol/kg injected intraperitoneally. The authors defined ataxia 2 as a "pronounced impairment of gait and motor incoordination but with the abdomen and pelvis still elevated."

Little information is available on the effects of cyclohexanol on humans. Nelson et al. (1943) found that exposure to 100 ppm cyclohexanol for 3-5 minutes caused irritation of the eyes, nose and throat in all subjects. Nonspecific disturbances of the autonomic nervous system were seen in 114 of 453 men and women exposed to cyclohexanol during caprolactam production (8/100 for controls). A 48-hour closed patch test with 4% cyclohexanol in petroleum produced no irritation (Rowe and McCollister, 1982). A worker exposed to a preparation containing butyl acetate and cyclohexanol complained of vomiting, coated tongue and slight tremors, but these effects could not be definitely attributed to cyclohexanol (Opdyke, 1975).

6. AQUATIC TOXICITY

6.1. ACUTE

Dawson et al. (1977) determined the acute toxicity of cyclohexanol to the freshwater bluegill sunfish, Lepomis macrochirus, and the saltwater tidewater silversides, Medidia beryllina. Under static exposure conditions said to be an indication of conditions following an acute spill, the 96-hour LC_{50} values were determined to be 1100 ppm in the bluegill and 720 ppm in the silversides. Veith et al. (1983) determined the 96-hour LC_{50} of cyclohexanol to be 704 ppm in the fathead minnow, Pimephales promelas, under flowthrough exposure conditions.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of cyclohexanol to aquatic animals were not located in the available literature as cited in the Appendix.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of cyclohexanol on aquatic plants were not located in the available literature as cited in the Appendix.

6.4. RESIDUES

Veith et al. (1983), cite a measured log octanol/water partition coefficient of 1.23 for cyclohexanol. This suggests that the bioconcentration potential of cyclohexanol is minimal; however, no measured residue data were located in the available literature to confirm this.

7. EXISTING GUIDELINES AND STANDARDS

The ACGIH (1980, 1983) recommends a TLV of 50 ppm in air (8-hour TWA) to reduce "objectionable irritation." This is the accepted value throughout the world except in Japan, which has a standard of 25 ppm (Rowe and McCollister, 1982).

8. RISK ASSESSMENT

No studies regarding the potential carcinogenicity or teratogenicity of cyclohexanol were available. Available data are inadequate for the assessment of the potential mutagenicity of cyclohexanol.

Chronic toxicity studies on cyclohexanol have not been conducted. Several subchronic inhalation studies have been reported, but the most adequate is that of Treon et al. (1943a). In this study, rabbits (four per group) were exposed to cyclohexanol vapor at 1229, 997, 272 and 145 ppm (4930, 4000, 1090 and 580 mg/m^3) for 6 hours/day, 5 days/week, for 5-11 weeks. The two highest concentrations resulted in a 50% mortality rate after 5 weeks (4930 mg/m^3) or 11 weeks (4000 mg/m^3) of exposure. At 1090 mg/m^3 (for 10 weeks) the animals gained weight, but there were observable effects of the treatment (conjunctival irritation and ear-vein distension). At the lowest concentration (580 mg/m^3 for 10 weeks) microscopic changes, which the authors described only as "evidence of toxic effects", were seen in the livers and kidneys of exposed animals. The animals exposed to 580 mg/m^3 continued to gain weight throughout the course of the study and no gross deleterious effects were observed. Since the description of the microscopic changes was inadequate to determine whether the lowest exposure tested represented a NOAEL, LOAEL or FEL, this study was considered inadequate for use in deriving an ADI.

Two other short-term studies are available. Male gerbils and house rats were administered s.c. doses of cyclohexanol (15 mg/kg/day) for 21 and 37 days, respectively (Tyagi et al., 1979). The major effects of cyclohexanol were weight reduction and histopathological changes in the testes, epididymis and seminal vesicles. Serum and hematological studies provided evidence that the general metabolic activities of treated animals were

unaffected. Male rabbits were treated orally with cyclohexanol diluted with olive oil at 25 mg/kg/day for 40 days (Dixit et al., 1980). The effects were similar to those seen with gerbils and house rats. Degranulation within hepatocytes, but no liver necrosis, was seen upon histological examination (livers were not studied in the report by Tyagi et al., 1979). The adverse effects described for male reproductive organs in both of these studies at the doses tested precludes the use of these data in the derivation of an ADI.

Two other subchronic studies are available as abstracts from the Russian literature. Voronin and Usol'tseva (1972) reported hypoxia and changes in copper, iron and nickel levels in lungs and serum in rats exposed to cyclohexanol at 43 mg/m^3, 5-6 hours/day for 100 days. Dobrinskii (1964) reported changes in ascorbic acid content and cholinesterase activity and in neurophysiological parameters when rats were exposed to 0.149 ppm cyclohexanol 24 hours/day for 87 days, followed by 6 days of semistarvation. The toxicological significance of these endpoints is not clear and the reliability of data taken from such abstracts is uncertain. Therefore, it is not recommended that these data be used to derive an ADI for humans.

9. REPORTABLE QUANTITIES (RQ) RANKING BASED ON CHRONIC TOXICITY

No studies regarding the teratogenicity and chronic toxicity of cyclohexanol were located in the available literature. One subchronic inhalation study (Treon et al., 1943a) and one subchronic oral study (Dixit et al., 1980) are available which report data that is potentially useful for RQ derivation.

The CSs calculated for cyclohexanol from the Treon et al. (1943a) inhalation are summarized in Table 9-1. The highest CS was derived from the effect associated with the 2nd high exposure level. Rabbits were exposed to 997 ppm (4000 mg/m^3) cyclohexanol for 6 hours/day, 5 days/week for 11 weeks. The human MED is calculated to be 1789.6 mg/day by expanding the exposure from 6-24 hours/day and from 5-7 days/week, by multiplying by body weight, animal breathing rate, correction factors and human body weight (70 kg), and by dividing by an uncertainty factor of 10 to reflect the subchronic duration. This MED corresponds to an RV_d of 1. The effect (50% mortality) is reflected by an RV_e of 10. The CS (calculated by RV_d x RV_e) is 10, which corresponds to an RQ of 1000.

The subchronic oral study with rabbits (Dixit et al., 1980) can be used to estimate a CS for oral exposure. The dose administered was 25 mg/kg. Dividing the dose by 10 to reflect the subchronic duration, multiplying by (rabbit weight/human weight)$^{1/3}$ [i.e. (1.13 kg/70 kg)$^{1/3}$] and then multiplying by 70 kg results in an MED of 44.2 mg/day. This corresponds to an RV_d of 3.0. The effect (reversible disruption of spermatogenesis) is reflected by an RV_e of 5. The CS (RV_d x RV_e) is 15 (Table 9-2).

TABLE 9-1

Composite Scores for the Toxicity of Cyclohexanol

Species	Route	Dose Level	Chronic Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Rabbit	inhalation	145 ppm (580 mg/m³) (6 hours/day, 5 days/week)	259.4	1.9	Slight degenerative changes in liver and kidneys	5	9.5	1000	Treon et al., 1943a
Rabbit	inhalation	997 ppm (4000 mg/m³) (6 hours/day, 5 days/week)	1789.3	1.0	50% mortality within 11 weeks	10	10	1000	Treon et al., 1943a
Rabbit	oral	25 mg/kg	44.2	3.0	Reversible disruption of spermatogenesis	5	15	1000	Dixit et al., 1980

*An uncertainty factor of 10 was applied to estimate a chronic exposure level.

TABLE 9-2

Cyclohexanol

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose[a]	1789.3 mg/day
Effect:	50% mortality
Reference:	Treon et al., 1943a
RV_d:	1.0
RV_e:	10
Composite score:	10
RQ:	1000

Route:	oral
Dose[a]	25 mg/kg
Effect:	reversible disruption of spermatogenesis
Reference:	Dixit et al., 1980
RV_d:	3.0
RV_e:	5
Composite score:	15
RQ:	1000

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*Equivalent human dose

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in July, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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